The dark side of innate and adaptive immunity - cytotoxic and dendritic cell lymphomas

...attack of the clones

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WA

Dr Vincent McGovern 1915-1983
The players

- Components of the innate and adaptive arms of the immune system
  - extreme form of immune dysregulation

- CD8+ (αβ+) T cells
- γδ+ T-cells
- NK cells
- NK-associated T-cells
- Dendritic cell (type 2) precursor
Why??

- Follicular lymphomas are boring
- Very different from B-cell lymphomas
  - least common of the uncommon (<2%)
  - diagnostically problematic (mimic other NHL)
    - phenotypic promiscuity
    - diagnostic armamentarium
  - clinically distinctive
    - extranodal, limited stage
      - tissue restricted lymphocyte subsets
    - aggressive, chemoresistant
    - hemophagocytic syndrome
    - chronic antigenic stimulation, impaired immunity
1. Review clinicopathological features
   – WHO 2001
   – WHO-EORTC (2005) classification for cutaneous lymphomas
2. Normal lymphocyte immunobiology
3. New data
4. CD4+ CD56+ hematodermic neoplasm
INNATE immunity

INNATE-LIKE
“Bridge” innate and adaptive

ADAPTIVE immunity

DENDRITIC CELLS
NK CELLS

γδ+ T CELLS
NKT CELLS
T_{reg} cells

αβ+ T CELLS
- CD8+
- CD4+

Blood
1^0
lymphoid tissues
2^0
Tissue-restricted

Macrophages, pmn, mast cells

B-1 B cells

B cells, plasma cells

- Specific tissue distributions -
- Site-specific homing mechanisms -
Natural killer lymphocytes

NK and NK/T lymphomas
Immunoregulatory cytokines chemokines (adaptive immunity)

Natural cytotoxicity non-MHC cytotoxicity (innate immunity)

Immunoregulatory cytokines chemokines (adaptive immunity)

NK CELL

TCR - G

CD3ε

CD56

NCR

CLR

costimulatory KIR

Perforin

granzyme TIA-1

Phenotypic promiscuity!
Natural killer receptors (NKRs)

Natural killer cell

Killer-activating receptor

Killer-inhibitory receptor

Ubiquitous molecule

MHC class I molecule

No attack

Normal cell

Abnormal cell lacking MHC class I molecules

Kill

Perforin and granzymes

NEJM 2000; 343:37-49
NK receptors

Most NK receptors are not specific for NK cells

- **HLA-recognising receptors**
  - Killer Ig-like receptors (KIR)
  - C-type lectin-like receptors (CLR)
    - CD94/NKG2 family heterodimers

- **Non-HLA binding**
  - NKG2D homodimer
  - Natural cytotoxicity receptors (NCR)
    - NK-specific: 2 NCRs only (NKp46; NKp30)
  - Costimulatory receptors
    - e.g. 2B4; NTBA (activ/inhib)
Diagnostic utility of NKR expression

- Abnormal patterns of NKR expression
  - restricted repertoires (KIR) indicative of pathological state, not necessarily lymphoma
    - receptor genes do not rearrange
  - transcripts may be of prognostic relevance
  - normal reference ranges to be established
    - correlation with other clonality studies
WHO

NK cell proliferations

E/nodal NK/T-cell lymphoma, nasal type

Aggressive NK cell leukemia
  Chronic NK-lymphocytosis
E/nodal NK/T-cell lymphoma, nasal type

- Asia, C & S America; American Indians
  - rare in West
- Upper respiratory tract - nasal, n/pharynx
  - rhinitis, bleeding, mass
  - bone destruction - high frequency
    - maxilla, orbit, palate
- Skin, subcutis, GIT, lung, testis, female genit.
  - skin second most common site
- Extranasal cases - more often advanced stage
Extranodal NK/T lymphomas

- Morphology heterogeneous, clinically irrelevant
  - Necrosis, apoptosis
    - death receptor activation: Fas-FasL, TRAIL →
      → caspase cascade → apoptosis
    - cytotoxic granule exocytosis
  - angio-invasion, angio-destruction
    - chemokines Mig and IP-10 endotheliotoxic (CXC family)

- Activated cytotoxic phenotype
  - Perforin+, Granzyme+ (cf. TIA-1+ only)

- EBER+ (site-, geography-dependent)
Extranodal NK/T-cell lymphoma, nasal type

- NKR expression
  - CD94/NKG2A+ majority
    - CD94 mRNA +ve ?? better prognosis than -ve
    - KIR+ minority of cases; restricted repertoire
- Cutaneous lymphocyte antigen+ (>50%)
  - cutaneous cases particularly
  - poor prognostic factor
- Del (6q); gains at 1p32-pter
  - multiple recurrent gains/losses
E/nodal NK/T-cell lymphoma, nasal type

- Aggressive, even stage 1E
  - early systemic spread, typically extranodal
    - skin, subcutis, GIT, testis, soft tissue; marrow
    - leukemic (aggressive NK cell leukemia)
  - chemoresistance - MDR-1 (P-glycoprotein)
  - hemophagocytic syndrome ~10% (TNFα; NFκB)
- 5 yr OS and DFS <40%; DXT mainstay of Rx
  - IPI of prognostic significance
  - no effect - age, stage, p53, cell size, EBER, Rx, lineage (Ng SB et al; Mod Pathol 2004)
Natural Killer-Like T-Cell Lymphomas: Aggressive Lymphomas of T-Large Granular Lymphocytes

By William R. Macon, Michael E. Williams, John P. Greer, Richard D. Hammer, Alan D. Glick, Robert D. Collins, and John B. Cousar

Natural killer (NK)-like T cells are major histocompatibility complex-unrestricted cytotoxic T cells that are surface CD3-positive, express NK-cell antigens, and rearrange their T-cell receptor. Most neoplasms arising from this T-cell subpopulation have been a chronic lymphoproliferative disease resembling virocytes. Azurophilic granules, ultrastructurally corresponding to cytoplasmic dense core and/or double density granules, were seen in all cases. T-cell clonality was shown in five tumors by Southern blot analysis, and three had abnormal karyotypes. Two untreated patients died 20

Nonnasal Lymphoma Expressing the Natural Killer Cell Marker CD56: A Clinicopathologic Study of 49 Cases of an Uncommon Aggressive Neoplasm


Expression of the natural killer (NK) cell antigen CD56 is uncommon among lymphomas, and those that do are almost exclusively of non-B-cell lineage and show a predilection for the nasal and nasopharyngeal region. This study analyzes 49 cases of nonnasal CD56+ lymphomas, the largest

CD56 POSITIVITY

Male predominance
Advanced stage, aggressive

EXTRANODAL - liver, spleen, intestine, lung, URT
Little or no peripheral adenopathy
Immunosuppressed
Aggressive NK-cell leukemia

- Japan, Asia >>> West (RARE!)
  - largest series 22 cases (Suzuki R, Leukemia 2004)
- Relatively young, fever, B symptoms, anemia
- Leukemic presentation
  - minority lymphoma-like
    - adenopathy, little or no blood involvement
- Hepatosplenomegaly; coagulopathy
  - frequent GIT, skin, nodes; marrow subtle or overt
  - large granular lymphocytosis
- Aggressive - death in months; HPS frequent
Aggressive NK-cell leukemia

- sCD3-, cCD3+, CD4-8-, CD56+
- TCR germline
- EBER+
- SKY and CGH studies
  - frequent 6q, 13q, 11q, 17p13 deletions
    (similar to NK/T lymphoma, nasal type)
  - translocations involving Xp21-pter; 8p23

Message:
- Don’t undercall as an indolent large granular lymphocytosis / leukemia
The mucosal immune system

Enteropathy type T-cell lymphoma
Enteropathy-type T-cell lymphoma (ETTL)

- Arises from phenotypically heterogeneous subsets of IELs
  - cytotoxic T lymphocytes
  - natural killer cells (rare)

- Coeliac disease - clinical or latent
  - HLA DQA1*0501; DQB*0201; DRB*0304
  - adults, recent onset
  - refractory sprue
  - ulcerative jejunitis
NORMAL

TCR$\alpha\beta$
CD3
CD8
CD103

MAJORITY

70%

COELIAC

TCR$\gamma\delta$
CD3
CD8
CD103

UP TO
30%

15%

REFRACTORY
SPRUE / UJ

TCR- (or $\gamma\delta$+)
sCD3-, cCD3+
CD4-, CD8-
CD103+

RARE

UNCOMMON

ETTL

TCR$\alpha\beta$

MAJORITY

‘Type A’

cCD3+
CD103

3-
8-(8+)

MINORITY

‘Type B’

cCD3+

3-

COELIAC

MAJORITY

RARE

UP TO
30%

15%

MALIGNANT

CLONAL

TCR$\gamma$-R

“Cryptic ETTL”

RARE

15%

CD8$\alpha\alpha$

CD56
Enteropathy-type T-cell lymphoma

- Localised disease typically
  - may disseminate
    - LN, liver, spleen, lung, skin
- Mass may be absent
  - ulcers, obstruct, perforate, bleed
- Enteropathic mucosa ~50%
  - proximal >> distal; affected by gluten free diet
- Aggressive course - death in months
- Not allintestinal T-NHL are ETTL !!
Enteropathy-type T-cell lymphoma

- **CGH and microsatellite studies**
  - >85% recurrent gains/losses at several loci
  - gains at 9q33-34 ~60%, both types A and B
    - C-ABL and NOTCH-1
  - >3 imbalances prognostically unfavorable
  - LOH at 9p21 one third cases (type A >> B)
    - site of suppressors p14/ARF, p15/INK4b, p16/INK4a
Cutaneous cytotoxic T-cell lymphoma (non-ALCL)

- Similar homing mechanisms as in intestine
- Skin-homing T cells express:
  - CLA: binds to E-selectin on cutaneous vascular endothelium
  - CCR4: binds to CCL17(TARC) expressed on cutaneous vascular endothelium
  - CCR10: ligates CCL27 on keratinocytes
Aggressive epidermotropic CD8+ CTCL

Localised or disseminated
- Patches, plaques,
- papulonodules, tumours
Ulceration
Adnexotropism, fat rimming
Extranodal spread
- lung, testis, CNS, oral
Median survival 32 mos
0% 5 yr survival

Prof. L Cerroni

Provisional entity WHO/EORTC 2005
Gamma-delta (\(\gamma\delta\)) T-cells
\(\gamma\delta^+\) T-cell lymphomas
$\gamma\delta^+ \ T \ cells$

- "Innate-like" lymphocytes
  - bridge innate and adaptive immune systems
  - rapid cytokine producers; cytotoxicity
  - important roles in
    - infection
    - immune regulation
    - immune surveillance

- Restricted tissue distribution
  - 5 - 15% of peripheral blood lymphocytes
  - 10 - 15% splenic red pulp
  - thymus, nodes, GIT, other mucosae, liver, skin
γδ+ T cells

- Lack recirculation
- Receptors of very limited diversity (Ig-like)
- No MHC restriction or Ag processing
- No clonal expansion
- Not a homogeneous population
  - most CD4-8-; IELs are CD8αα+
  - subclassification according to V segment usage
    - Vδ1 - naïve/fetal T-cell phenotype (CD45RO-)
      - spleen, thymus, germinal centres of nodes
    - Vδ2 - memory/adult phenotype (CD45RO+)
      - blood, interfollicular nodes & tonsils, skin
γδ+ T-cell lymphomas

- Sites
  - hepatosplenic (immature Vδ1+) - WHO 2001
  - mucocutaneous and epithelial sites (mature Vδ2)
- Limited stage, but aggressive
  - necrosis, apoptosis
  - hemophagocytic syndrome
- Mimic and overlap other cytotoxic lymphomas
  - SPTCL, NK/T nasal type, ETTL
Hepatosplenic T-cell lymphoma

- Most from naïve splenic $\gamma\delta+$ T-cells ($V\delta 1+$)
- Young adult males
  - hepatosplenomegaly
  - thrombocytopenia, anemia, leukopenia (~45%)
  - no adenopathy; other sites rare
  - leukemic presentation rare
- $\alpha\beta+$ cases occur (females; wider age range)
- Chronic Ag stimulation + altered immune state
  - post-organ transplant, SLE, HD, chronic Hep B
Hepatosplenic T-cell lymphoma

- Marrow+, but may be subtle, sinusoidal
- Lymphocytosis minor or absent at Dx
  - blastic change +/- leukemic terminally
- Aggressive course - poor chemosensitivity
  - median survival 16 months
  - indolent, relapsing prodrome in some
- Must exclude mimics
  - T-LGL
  - aggressive NK leukemia
  - others
Nonhepatosplenic γδ T-Cell Lymphoma: A Subset of Cytotoxic Lymphomas With Mucosal or Skin Localization

By Bertrand Arnulf, Christiane Copie-Bergman, Marie-Hélène Delfau-Larue, Anne Lavergne-Slove, Jacques Bosq, Janine Wechsler, Michel Wassef, Claude Matuchansky, Bernard Epardeau, Marc Stern, Martine Bagot, Felix Reyes, and Philippe Gaulard

Human γδ T lymphocytes represent a minor subset of T cells in the peripheral blood, which exhibit a limited diversity and a tissue-restricted repertoire in contrast to their broad specificity. Most postthymic neoplasms that arise from this T-cell subpopulation belong to the hepatosplenic γδ lymphoma entity. Only a few cases of nonhepatosplenic γδ lymphomas have been described in detail previously. This study presents the clinicopathologic features of 11 consecutive cases of nonhepatosplenic γδ lymphoma. All were characterized by mucosal or skin initial involvement: nasal cavity (n = 3), gastrointestinal tract (n = 3), skin (n = 3), lung (n = 1), larynx (n = 1). Most patients presented with B symptoms (eight of 11), without peripheral lymphadenopathy and bone marrow involvement. A past history of chronic antigen exposure was noted in six cases, and four patients had features of immune deficiency. On histology, they were classified as pleomorphic tumors. Features of epitheliotropism and angiocentrisit was observed in most cases. Tumor cells had a CD2+, CD3+, T-cell receptor (TCR)δ−1+, βF1− phenotype. They were CD5− (9 of 10) and CD4−/CD8− (9 of 10) or CD8+ (1 of 10). A clonal γ-chain gene rearrangement was detected in all tested cases (9/9). All cases had an activated cytotoxic T-cell intracellular antigen-1 (TIA-1)+, granzyme B+ phenotype. Epstein-Barr virus (EBV) sequences were detected in six cases by in situ hybridization (ISH). Despite an aggressive clinical course, complete remission was obtained in three patients, and one of the latter required a peripheral blood stem-cell transplantation.

Clinicopathologically similar to other cytotoxic lymphomas at the same sites

- Activated cytotoxic phenotype
  - cf. hepatosplenic

Primary nodal - uncommon
- Lymphoblastic 50%
- T-cell LGLL - uncommon

Skin/subcutis
- GIT, lung, URT
- Testis, breast, thyroid
Gamma-delta T-cell phenotype is associated with significantly decreased survival in cutaneous T-cell lymphoma

Jorge R. Toro, David J. Liewehr, Nina Pabby, Lynn Sorbara, Mark Raffeld, Seth M. Steinberg, and Elaine S. Jaffe

BLOOD 2003; 101:3407-3412

33 cases

γδ phenotype: independent predictor of decreased survival

- Extremities, trunk
- Mucosal, extranodal
  - nodes, spleen, marrow uncommon
- HPS in SPTCL-like cases
- Chemoresistant
  - 15 mos median survival
- Mature, cytotoxic, Vδ2+
  CD4-, CD8- (few CD8+)
  CD56+/-; EBER-
Subcutaneous panniculitis-like T-cell lymphoma

(WHO-EORTC 2005)
Subcutaneous panniculitis-like T-cell lymphoma

- Mainly young adults, indurated s/cutaneous nodules/plaques, extremities > trunk > face
  - extracutaneous spread rare

- Systemic symptoms frequent;
  - haemophagocytic syndrome up to 50%

- Aggressive typically
  - median survival 27 mos (Go & Wester, review 2004)
  - high dose chemo/stem cell Tx effective in some
  - some indolent, remitting/relapsing with chemoRx,
    • related to phenotype
  - rarely may disseminate to nodes, e/nodal sites
Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)

Pre-2005 view

2 forms of SPTCL

- $\alpha\beta^+$ SPTCL (75%)
- $\gamma\delta^+$ SPTCL (25%)
BLOOD 2005; 105:3768-3785

WHO-EORTC classification for cutaneous lymphomas


Primary cutaneous lymphomas are currently classified by the European Organization for Research and Treatment of Cancer. The classification of different types of cutaneous B-cell lymphomas has resulted in considerable debate and confusion. During recent classification schemes, in addition, the relative frequency and survival data of 1905 patients with primary cutaneous lym-
a neoplasm of plasmacytoid dendritic cell precursors

Plasmacytoid dendritic cell (pDC) precursor

plasmacytoid monocytes

DC2

CD4+ CD56+ hematodermic neoplasm
(Blastic NK-cell lymphoma)

WHO-EORTC 2005
CD34+ progenitor

Myeloid progenitor

IL4
GMCSF

CD14+
CD11c+

Monocyte

TLR 2,3-6,8 signalling

TH1

TH2

TLR 7,9 signalling

CD123+

DC1

IL12

DC2

IFNα

IL3

CD40L (CD154)

CD123+
CD14-
CD11c-

Plasmacytoid DC

Lymphoid progenitor

CD34+ progenitor

T CELL ACTIVATION
The Enigmatic Plasmacytoid T Cells Develop into Dendritic Cells with Interleukin (IL)-3 and CD40-Ligand

By Géraldine Grouard, Marie-Clotilde Rissoan, Luis Filgueira, Isabelle Durand, Jacques Banchereau, and Yong-Jun Liu

From *Schering-Plough, Laboratory for Immunological Research, 69571 Dardilly, France; and ‡Institute of Anatomy, Division of Cell Biology, University Irchel-Zurich, 8057 Zurich, Switzerland

*J Exp Med 1997; 185:1101-1111

Summary
A subset of CD4+CD11c-CD3- blood cells was recently shown to develop into dendritic cells when cultured with monocyte conditioned medium. Here, we demonstrate that CD4+ CD11c-CD3- cells, isolated from tonsils, correspond to the so-called plasmacytoid T cells, an

Plasmacytoid monocytes migrate to inflamed lymph nodes and produce large amounts of type I interferon

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Nature Med 1999; 5:919-923
Blastic Natural Killer Cell Leukemia/Lymphoma: A Clinicopathologic Study

*Am J Surg Pathol 1997; 21(10):1223-1230*

Joseph A. DiGiuseppe, M.D., Ph.D., Diane C. Louie, M.D., James E. Williams, M.D., David T. Miller, M.D., Ph.D., Constance A. Griffin, M.D., Risa B. Mann, M.D., and Michael J. Borowitz, M.D., Ph.D.

CD4+ CD56+ Cutaneous Neoplasms: A Distinct Hematological Entity?

*Am J Surg Pathol 1999; 23(2):137-146*

CD4+ CD56+ hematodermic neoplasm (Blastic NK-cell lymphoma) - WHO/EORTC

- Rare, aggressive
- Cutaneous
  +/- leukemic
- M>F, median 60s
- Violaceous skin plaques, nodules, non-ulcerating
- >60% stage IV at Dx

- marrow (80%)
- LN (>50%)
- spleen/liver (20%)
CD4+ CD56+ hematodermic neoplasm (Blastic NK-cell lymphoma) - WHO/EORTC

- Leukemic - often at Dx, or develops rapidly
- Poor prognosis - median survival 13 mos
- Indolent course in some ?predictable
  - possible favorable factors
    - skin-confined; age <40; TdT+
    - Rx with leukemia-type regimes
    - induction of remission + allogeneic SCT
CD4+ CD56+ hematodermic neoplasm (Blastic NK-cell lymphoma)

- Lineage negative (T-, B-, Myeloid, NK-)
- CD45RA+; Granz B; TdT -/+ 
- Antigen receptor genes germline
- Cutaneous lymphocyte antigen +ve 
- BDCA-2, BDCA-4 positive (novel markers)
- del(5q)
CD4+ CD56+ hematodermic neoplasm (Blastic NK-cell lymphoma)

- Association with MDS or MPD (15-20%)  
  - AMML evolution in small subset
- Acquisition of some myeloid markers during disease progression, e.g. CD33
- ?? Relation to myelo-monocytic lineage  
  - plasticity; common ancestry pDC, Myeloid, NK
Malignant lymphoma of plasmacytoid T-cells
Morphologic and immunologic studies characterising a special type of T-cell

*Hans Konrad Muller-Hermelink et al*


(Myelomonocytic leukemia 3 mos after Dx)
Nodal and Extranodal Tumor-forming Accumulation of Plasmacytoid Monocytes/Interferon-producing Cells Associated With Myeloid Disorders

William Vermi, MD,* Fabio Facchetti, MD, PhD,* Stefano Rosati, MD, † Federica Vergoni, MD,* Elisa Rossi, MD,* Silvana Festa,* Daniele Remotti, MD, † Piergiovanni Grigolato, MD,* Giovannino Massarelli, MD,§ and Glauco Frizzera, MD‖


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- pDC accumulations in Nodes, Marrow, Skin
- Clonal identity 1 case by FISH
  AML and pDC cells both with monosomy 7
- Most CD56 negative
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